REMARKS

Favorable reconsideration of this application, in light of the preceding amendments and following remarks, is respectfully requested.

Claims 1-14 are pending in this application. No claims have been amended, added or cancelled. Claim 1 is the sole independent claim. Claims 7-10 and 14 have been withdrawn from consideration.

Rejections under 35 U.S.C. § 103

Antananvich in view of Brauker and Wang

Claims 1-6 and 11-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,372,244 to Antananvich et al. (hereinafter "Antananvich") in view of U.S. Patent No. 5,782,912 to Brauker et al. (hereinafter "Brauker") and U.S. Publication No. 2003/0153981 to Wang et al. (hereinafter "Wang"). Applicants respectfully traverse this rejection for the reasons detailed below.

The outstanding Office Action on page 8, lines 4-5, acknowledges that Antananvich and Brauker fail to disclose a surface coating of a bioactive metal and relies on the teachings of Wang for this feature of claim 1.

Antanavich discloses a bioartificial implant (thin sheet bioartificial implant, Fig. 1) comprising a semipermeable barrier (coat 4; column 19, lines 10-20, 54-56; column 20, lines 55-61; column 21, lines 27-28). Antanavich also discloses that the semipermeable barrier or coating can be covered by an alginate overcoat to enhance the biocompatibility of the implant (column 19, lines 56-58; column 21, lines 27-28).

Antanavich further defines that the biocompatibility of the alginate overcoat implies that the material by itself should not promote cellular adhesion, coverage by collagen fiber layer or overgrowth of endothelial cells (page 4, lines 41-50). In clear contrast, such phenomena occurring in connection with some biocompatible

membranes is not desirable for the cellular implants of Antanavich since they will starve the cells in the implant (column 4, lines 45-46).

Applicants agree with the Examiner that Antanavich does not disclose that the semipermeable barrier has a surface coating of a bioactive metal. In clear contrast, the alginate coat of Antanavich has a further alginate overcoat.

Brauker discloses a bioartificial implant (sensor 80) comprising a semipermeable barrier (second membrane 50; column 3, lines 64-66; column 4, lines 8-12; column 13, lines 24-33). Brauker further discloses that a first membrane (membrane 42) surrounds the second membrane (column 3, lines 62-63; column 13, lines 8-10). This first membrane is a porous polymer membrane having a specific average nominal pore size and average strand size to induce close vascularization (column 3, lines 62-63; column 4, lines 50-56; column 7, lines 40-43). The second, innermost membrane prevents passage of cells through the membrane, whereas the first, outermost membrane induces close vascularization (column 3, lines 62-66). This induction of vascularization is due to the entry of non-activated rounded macrophages in the cavities of the first membrane (column 4, lines 30-36).

Applicants agree with the Examiner that Brauker also does not disclose that the semipermeable barrier has a surface coating of a bioactive metal.

Wang discloses the production of a porous metal scaffold for orthopedic implants and not for any cellular implants (paragraphs 16, 17, 84). The scaffold is produced by providing a polymer foam and forming a skin of titanium on the polymer foam by low temperature arc vapor deposition (paragraphs 22-23, 41-42, 90, 102). The resulting structure is heated at a high temperature (>400 °C) to decompose the polymer foam and form a green foam (paragraphs 24, 43, 92, 104, 106). The sensitive green foam is pre-sintered at about 1315 °C (paragraphs 44, 93, 110) and then thickened. The thickening of the green foam is achieved by adding a binder solution

and then depositing titanium particles (paragraphs 25, 35-37, 45, 93, 111-112, 114). The particles are bond to the green foam by sintering at about 1425-1530 °C to form the porous metal scaffold (paragraphs 46, 94, 115). The application of titanium particles to the green foam reduces the pore size of the green foam (paragraphs 25, 27, 53, 93, 114). Wang thus discloses a technique for forming a porous metal scaffold for orthopedic implants and which improves the in-growth of bone and promotes the initial press-fit stability (paragraphs 16, 88).

The Examiner correctly points out that Wang states that the titanium material used therein is biocompatible. However, biocompatibility as defined according to Wang is not the same definition as is given by Antanavich. In clear contrast, according to Wang, the porous titanium scaffold should *promote* in-growth of tissue, e.g., bone (paragraphs 9, 88). This means that the porous titanium scaffold with the titanium particles is designed to facilitate in-growth of bone tissue.

However, according to Antanavich such in-growth of tissue is not desirable in the case of cellular implants as disclosed therein. In clear contrast, all such tissue in-growth should be prevented as much as possible to reduce the risk of starving cells in the cellular implant. It is for this reason that Antanavich has the particular overcoat that reduces tissue in-growth.

Furthermore, Wang discloses that the porous titanium foam with the titanium particles applied thereon needs to be heated or sintered in order to sufficiently bond the particles to the foam (paragraphs 37, 46, 93, 111, 114). This bonding is performed at a temperature over 1000 °C (paragraphs 46, 94, 110, 115). If the technique of Wang, hence, would have been applied to the cellular implant of Antanavich as suggested, the alginate-based cellular implant and the sensitive pancreatic islets therein would have been exposed to temperatures of over 1000 °C, which would have totally burned off and evaporated the alginate implant and instantly

killed all pancreatic islets. The deposition and binding technique as disclosed by Wang is therefore only possible in connection with orthopedic implants, where the substrate is a metal substrate and does not enclose any living cells.

Thus, given the objectives of Antanavich of providing a cellular implant with improved biocompatibility in terms of reducing tissue in-growth following the implantation in the host, the person skilled in the art would not have applied the disclosure of Wang to the cellular implant of Antanavich. In clear contrast, the technique of Wang promotes tissue in-growth and therefore would contradict the objective of Antanavich. Therefore, one of skill in the art would not be motivated to apply the surface coating of a bioactive metal as disclosed in Wang to the cellular implant of Antanavich.

A further problem with Wang is that the titanium particle deposition as disclosed therein will reduce the pore size of the porous substrate (paragraphs 37, 53, 93). However, Antanavich stresses the importance of having a cellular implant that allows sufficient transportation of oxygen and nutrients into the cells of the cellular implant and transport of molecules, such as insulin, produced by the cells. The alginate coat of Antanavich has therefore been carefully selected to provide sufficient permeability to support viability of the enclosed cells but inhibiting diffusion of large molecules and cells. Applying the titanium particles according to Wang would negatively affect the permeability of the alginate coat of Antanavich since Wang *explicitly* discloses that the titanium particles will *reduce* the pore size of the porous substrate onto which the titanium particles are applied.

This pore-blocking feature of Wang further illustrates that one of skill in the art would not be motivated to apply the surface coating of a bioactive metal as disclosed in Wang to the cellular implant of Antanavich.

In addition, Applicants submit that one skilled in the art would never have

combined Wang with Antanavich for, among others, the following reasons:

- The titanium particles and porous scaffold of Wang promotes tissue in-growth. Antanavich stresses the importance of an implant overcoat that prevents any tissue in-growth, which otherwise would starve the cellular implant.
- The titanium particles of Wang need to be bonded to the porous substrate with heating over 1000 °C. Such high bonding temperature would evaporate the complete cellular implant of Antanavich and kill all cells therein.
- The titanium particles of Wang reduce the pore size of the porous substrate. It is crucial for cell survival and viability of the cellular implant of Antanavich that the passive transport of oxygen and nutrients into the implant interior and the cells therein is not impeded or blocked. A reduction in pore size would significantly reduce this transport and negatively affect the survival of the cells.
- Wang is directed towards an orthopedic metal implant, whereas Antanavich discloses a cellular implant comprising living tissue.
- The technical effects achieved by the titanium particle coating of Wang in terms of improved tissue in-growth, promoted initial press-fit stability and greater frictional interference to bone have no connection and does not provide any advantageous effects to the cellular implant of Antanavich.

Applicants further submit that even if Antanavich and Wang could be combined, the combination still does not arrive at the bioartificial implant as recited in claim 1. According to claim 1, the semipermeable barrier has a surface coating of a bioactive metal, where the surface coating is permeable to *not* interfere with the

semipermeability of the semipermeable barrier. The titanium particles of Wang reduce the pore size of the underlying porous substrate and thereby *interfere* with the semipermeability of the porous substrate.

With respect to the combination of Brauker and Wang, Wang explicitly discloses that the titanium particles fill the pores and cavities of the porous scaffold when applied on the substrate (paragraph 53). If such titanium particles would have been applied to the implant of Brauker, the peripheral cavities of the first membrane would be filled with the titanium particles. However, the positive effects of close vascularization obtained with the implant of Brauker are due to the entry of non-activated macrophages in the peripheral cavities.

If titanium particles according to Wang would have been applied to the implant of Brauker, the titanium particles would fill a substantial part of the peripheral cavities and thereby block and prevent entry of non-activated macrophages in these cavities. The positive effects in terms of close vascularization, which is the objective of Brauker, would then be absent. The transport of oxygen and nutrients from the blood in the vascular tissue into the cells of the implant and the transport of waste products away from the implant are also significantly reduced, which negatively affects the survival and viability of the cells in the implant.

Furthermore, Wang discloses that the porous titanium foam with the titanium particles applied thereon needs to be heated or sintered in order to sufficiently bond the particles to the foam (paragraphs 37, 46, 93, 111, 114). If the technique of Wang, hence, would have been applied to the implant of Brauker as suggested, the polymer-based implant and the sensitive cells therein would have been exposed to temperatures of over 1000 °C. However, this would have totally burned off and evaporated the polymer implant and instantly killed all cells. The deposition and binding technique as disclosed by Wang is therefore only possible in connection with

orthopedic implants, where the substrate is a metal substrate and does not enclose any living cells.

Therefore, Applicants submit that one skilled in the art would not have applied the technique of Wang to the implant of Brauker since the skilled person would conclude that such a combination reduces the close vascularization around the membrane and reduces the viability of the cells within the implant.

In addition, Wang discloses that the particular titanium scaffold with the titanium particles induces in-growth of bone tissue into the scaffold, which is advantageous for the orthopedic implant of Wang but not for the implant of Brauker. If the implant of Brauker would be implanted close to bone tissue in the host, the person skilled in the art would, from the disclosure of Wang, conclude that bone would grow into an implant designed according to a combination of Brauker and Wang. However, bone tissue would effectively prevent close vascularization around the implant, which further emphasizes that one skilled in the art would not have been led to combine Brauker with Wang.

In addition, Applicants submit that one skilled in the art would never have combined Wang with Brauker for, among others, the following reasons:

- The titanium particles and porous scaffold of Wang promotes tissue in-growth. Brauker stresses the importance of close vascularization around the implant. In-growth of bone would block such close vascularization.
- The titanium particles of Wang need to be bonded to the porous substrate with heating over 1000 °C. Such high bonding temperature would evaporate the implant of Brauker and kill all cells therein.
- The titanium particles of Wang reduce the pore size of the porous substrate and fills up pores and cavities of the substrate. It is crucial for the close vascularization effect of Brauker that non-activated macrophages

can enter the peripheral cavities of the implant. If titanium particles are present in the cavities the macrophages cannot enter and no induction of close vascularization is obtained. A reduction in pore size would also significantly reduce the transport of oxygen and nutrients over the membrane and negatively affect the survival of the cells.

- Wang is directed towards an orthopedic metal implant, whereas Brauker discloses an implant comprising living tissue.
- The technical effects achieved by the titanium particle coating of Wang in terms of improved tissue in-growth, promoted initial press-fit stability and greater frictional interference to bone have no connection and does not provide any advantageous effects to the implant of Brauker.

Applicants further submit that even if Brauker and Wang could be combined, the combination still does not arrive at the bioartificial implant as recited in claim 1. According to claim 1, the semipermeable barrier has a surface coating of a bioactive metal, where the surface coating is permeable to *not* interfere with the semipermeability of the semipermeable barrier. The titanium particles of Wang reduce the pore size of the underlying porous substrate and thereby *interfere* with the semipermeability of the porous substrate.

Furthermore, column 14, lines 1-20 of Brauker states that it is the three dimensional structure of the membrane that seems to be important for the close vascularization effect. The section further lists a variety of polymer materials that are believed to achieve similar effects as the membrane polymers tested in the document. Brauker continues by speculating that the disclosed effects might be achieved with known biocompatible ceramic and metal implants if these can be manipulated to provide the same three dimensional structures as the implant of Brauker. Applicants submit that this disclosure amounts to nothing more than speculations and further

does not define how such ceramic or metallic implant can indeed be manufactured to have the same three dimensional structures as disclosed in Brauker.

Furthermore, even if it indeed would have been possible to manufacture such a ceramic or metallic material, the person skilled in the art would still not have been guided towards applying the techniques of Wang to such an implant. For instance, the crucial peripheral cavities of the ceramic/metallic membrane would then be filled with titanium particles as disclosed by Wang. This means that the particles would block the entry of any non-activated macrophages into the membrane and no induction of close vascularization is achieved. Filling pores/cavities with titanium particles additionally negatively affects the passive transport of oxygen, nutrients and waste products over the membrane and thereby negatively affects the survival of any cells in the membrane.

The titanium particles still need to be attached to the ceramic or metallic membrane material by heating at temperatures above 1000 °C. Even if the ceramic/metallic material might endure such high temperatures, any cells within the implant would still instantly die.

For all of the above reasons, Applicants respectfully submit that the techniques disclosed by Wang are incompatible with the bioartificial implant of Antanavich and Brauker, and therefore, cannot render claim 1 obvious.

Claims 2-6 and 11-13, dependent on independent claim 1, are patentable for the reasons stated above with respect to claim 1 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 1-6 and 11-13 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the above remarks and amendments, the Applicants respectfully submit that each of the pending objections and rejections has been addressed and overcome, placing the present application in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to contact the undersigned.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Erin G. Hoffman, Reg. No. 57,752, at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 08-0750 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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